“Studies on Antimicrobial and Anticancer Potential of Actinomycetes Isolated from Forest Soil”

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"Studies on Antimicrobial and Anticancer Potential of ActinomycetesIsolated from Forest Soil"

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1. Abstract :

The worldwide growing concern about antimicrobial resistance among clinically important bacterial and fungal pathogens address the need for novel antibiotic compounds to overcome the challenges associated with treatment of drug resistant microbial infections. In addition to this,increasing emergence of drug resistant cancer cells , limited efficacy of available chemotherapeutic drugs and economic burden for treatment are serious concerns of recent era. Actinomycetes are predominant producers of bioactive molecules and they have proved their potential in last few decades in terms of antibacterial, antifungal, anticancer, immunomodulators and enzyme inhibitors. The research on isolation of actinomycetes from diverse ecosystems in search of new, safe and potent antibiotic compounds has been recorded in literature since long back. Terrestrial environments are more explored and studied for bioactive compound producing actinomycetes . As a result, frequency of isolating repeated strains has been documented several times. This indicates the need for selecting new and unexplored environments for isolation of actinomycetes with bioactive potential. With this view, in the present study, forest soil of Painganga wildlife sanctuary, Maharashtra, India is selected for studying diversity and characteristics of actinomycetes with antibacterial and anticancer potential. This area is understudied and represent diverse ecosystem rich in versatile flora and fauna. The forest soil is cultivated with medicinally important plants such as *Terminaliaarjuna, Phyllanthus emblica, Neolamarckia cadamba, Tinospora cordifolia, Buchanania cochinchinensis, Anogeissus latifolia, Terminalia bellirica, Madhuca longifolia, tree, Moringa, Haldina cordifolia* etc. Hence it is expected that the actinomycetes growing in this soil area demonstrate unique bioactive potency. With this aim, the present study is planned to isolate, identify and characterize actinomycetes from forest soil of Painganga Sanctuary, to optimize the production process, carry structural elucidation of bioactive metabolite and quantify the antimicrobial and anticancer activities. The exploration of actinomycetes from this uninvestigated forest ecosystem of Maharashtra, India will be biotechnologically relevant in drug discovery programs.

2. Introduction :

Antimicrobial drug resistance (ADR) is one of the greatest challenges facing healthcare systems and hence became a serious public health problem worldwide. The presence of antibiotic-resistant strains was initially confined to the hospital environment. However, their widespread appearance in different environments is posing a serious threat to mankind. There are several reasons contributing for this transformation and includes globalization, lack of effective antimicrobial drug, overuse of antibiotics, and use of broad-spectrum antibiotics along with inclusion of antibiotic resistance genes within bacterial populations. Many gram-positive and gram-negative bacterial species that were once considered harmless commensals have now evolved and emerged as serious pathogens that are resistant to the common antibiotics typically used to treat nosocomial and community-acquired infections (Sayed et al.,2023). Among multidrug resistant bacteria *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter sp.* are listed as priority pathogens by WHO because they are now the most frequent global cause of skin and soft tissue infections (Sayed et al.,2023).

Many studies have reported that diseases caused by multiple drug resistant (MDR) pathogens rank among the world's leading causes of morbidity and mortality (Reisman et al., 2017).Infections with MDR bacteria, especially by priority pathogensare extremely difficult to treat and can spread throughout hospital or community environments (Santajit , et al., 2016). As a result, the WHO has established an urgent priority list for new antibiotic discovery (Sayed et al.,2023). The increasing suffering of patients with infectious diseases caused by pathogenic microorganisms, especially MDR species, prompted the need to discover novel antibiotics by screening microorganisms from natural sources (Danquah , et.al. 2022.).

Cancer is most non communicable disease contributing 1 in 6 deaths for morbidity and mortality worldwide(WHO ,2020). Cancerfatality rate in low and mid income countries are vulnerable where, diagnosis is made at progressive stages of cancer.Among different types of cancer breast cancer gained worldwide attention as accounting for 13.5% of all cancer cases and 10.6% of all deaths in India alone (Int- agency 2020). According to world cancer report (2020),the most important preventive measures for control of breast cancer is early detection and fast treatment (Int- agency 2020). Chemoresistance is the principle issue in the treatment of breast cancer patients. It is challenging and complicated to understand the mechanism of resistance in breast cancer. Hence a search for additional treatment

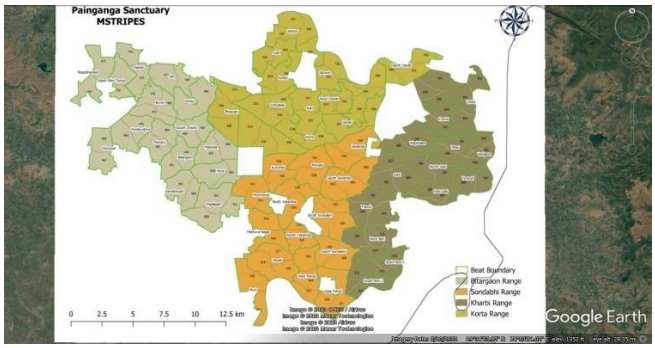
regimens is the utmost need to overcome the drug resistance and improve treatment strategies .This can be achieved through isolation and identification of novel and effective anticancer agents and using combined drug therapy approach(Ji et.al.,2019). Microbial diversity is a major frontier and future source for the biotechnology sector (Pramanik et al., 2019). Soil microorganisms provide an excellent resource for the isolation and identification of therapeutically important products. Among them, actinomycetales are an important group(Bérdy J. et.al. 2005).

Actinomycetes are a group of microbes widely distributed across the world's natural ecosystems and are especially valuable for their organic cycling role (Javed et al., 2020). Actinomycetes have unique bioactive metabolites, including antibiotics, enzymes, and plant growth factors (Dimri et al., 2020, Gunasinghe et al., 2020). Several studies showed Actinomycetes have vast range of biomedical applications such as antibacterial (Kurnianto et al., 2020), antibiofilm (Mulya and Waturangi 2021), antifungal (Wei et al., 2020), and anticancer (Rajivgandhi et al., 2020) activities. It has been reported that over 10,000 bioactive secondary metabolites are produced by actinomycetes, accounting for 45% of all discovered bioactive microbial metabolites, with approximately 7600 of the actinomycetes compounds produced by *Streptomyces* spp (Berdy J.et.al.2005). Many of these secondary metabolites are clinically useful antitumor drugs, such as anthracyclines (aclarubicin, daunomycin, and doxorubicin), peptides (bleomycin and actinomycin D), aureolic acids (mithramycin), enediynes (neocarzinostatin), antimetabolites (pentostatin), carzinophilin, and mitomycin(Olano et.al.2009,Olano et al., 2009; Newman et al., 2007.). It is therefore imperative that the search for novel natural microbial products be continued in underexplored habitats such as forest ecosystems, marine environments and glaciers. It has been hypothesized that since these microorganisms can sustain in these environments, some species may produce novel bioactive compounds for their survival, which could also serve as a source of new pharmaceutical compounds. The search for novel antimicrobial and anticancer drugs is an utmost priority, due to associated high toxicity and undesirable side effects of existing drugs that have increased the demand for drugs with fewer side effects and/or with greater therapeutic efficiency against drug resistant microbes and tumors.

Study area:

Painganga wild life sanctuary, a reserved forest located in Unmarked tehsil of Yavatmal District of Maharashtra state,India. It derives its name from the Painganga river which borders the sanctuary on its three sides. Sprawling area about 402 sq .km. exquisite

combination of southern mixed deciduous forest and teak forest ,along with diverse flora and fauna. Due to heavy rainfall and the surrounding Painganga river reservoir, many trees grow in the sanctuary area, including Arjun (*Terminalia arjuna*), Amla (*Phyllanthus emblica),* Kadamba *(Neolamarckia cadamba),* Gulvel *(Tinospora cordifolia),* Charoli *(Buchanania cochinchinensis),* Chinch *(tamarind),* Dhavda *(Anogeissus latifolia),* Behda *(Terminalia bellirica),* Moha *(Madhuca longifolia),* Sag *(drumstick tree, otherwise moringa) and* Haldu *(Haldina cordifolia).*There are about 200 species of herbs in the sanctuary, also reeds and grasses (for example, *kusali, khas, tirkadi, pavanya, marvel*).



Hypothesis:

The present study is planned to study the unexplored soil habitats of Painganga forest ecosystems of Maharashtra, India to find presence of previously undescribed actinobacteria with the capability to produce diverse antimicrobial and anticancer metabolites that may be explored to overcome the rapidly rising global concern about antibiotic resistance.

3. Review of literature :

Microbial metabolites produced especially by actinomycetes have been the basis for the synthesis of many antibiotics (Promnuan et al., 2020) hence making this group of organisms highly important in the medical and pharmaceutical sectors. The metabolites of actinomycetes have not only exhibited antimicrobial activity but have also shown anti-tumour, anti-viral, anti-cancer anti-inflammatory as well as immunosuppressive activities (Rammali et al., 2022; Gomes et al.,2018; Shukla, 2015)

Against both Gram positive and Gram negative multiple antibiotics resistant bacteria the *Streptomyces* spp. *Str1* shown antibacterial properties and thus it is a potential candidate for the development of promising antibacterial agents (Akpona et.al,2023).Actinomycetes were isolated from various unexplored regions from glaciers to terrestrial, marine habitathaving antibacterial activity. In which representative genera like *Nocardia,*and some new actinomyces species were isolated like *Friedmanella antarctica*

gen. nov., sp. nov., Friedmanella lacustris sp. nov., Nocardiopsis aurantiacus, Modestobacterium multiseptatum gen. nov., sp.nov having antimicrobial activity against *Bacillus subtilis ATCC 6633* reported(Nedialkovaet.al.,2004-05). The isolation method for rare actinomycetes genera *Actinoplanes, Actinokineospora, Acrocarpospora, Actinosynnema, Actinomadura, Amycolatopsis, Catenuloplanes, Cryptosporangium, Dactylosporangium, Kineosporia, Kutzneria, Microbispora, Micromonospora, Microtetraspora, Nocardia, Nonomuraea, Thermomonospora, Pseudonocardia, Thermobifida, Saccharomonospora, Spirilliplanes, Streptosporangium, and Virgosporangium* in Japanese soil was developed by combining pretreatment with suitable media supplemented with specific antibiotic.(Hayakawa 2008)

It has been revealed that actinomycetes strains had both broad spectrum and narrow spectrum of activity against the pathogenic isolates among that *Streptomycetes* have maximum antimicrobial activity .The isolates *Streptoalloteichus (H5) and Actinodassonvillei (B2)* from wetland soil samples showed the maximum inhibition zone of 35 mm against *S. bareilly*(George et.al. 2012). *Streptomyces* sp. Have minimum activity against *Staphylococcus aureus (ATCC 29213), Pseudomonas aeruginosa (ATCC 27853), Escherichia coli (ATCC 25922) and Klebsiella pneumonia (ATCC 4352)*(Sethi et.al.2013) .The antimicrobial activity of actinomycetes against some multidrug-resistant pathogens such as including methicillin-resistant *Staphylococcus aureus (MRSA) and Escherichia coli* have been reported (Sharma et.al.2011) from Punjab and Himachal Pradesh localities.

The strain of Streptomyces sp. 211726 was isolated from mangrove rhizosphere soil of *Heritiera globosa* collected in Wenchang, China , able to produce the seven new compounds azalomycin F analogue .They also showed moderate cytotoxicity against human colon tumour cell HCT-116 in vitro (Yuan et.al.2013). In anotherunexplored area of Sundarbans mangrove ecosystem nearly 54 *Actinomycetes* spp has been found, out of which only 9 isolatespossess antimicrobial activity, while other possess antioxidant activity(Sengupta, et.al.2015). Other mangrove derived *Streptomyces* sp. MUM265 showed cytotoxicity against colon cancer cells by the reduction in cell viability of Caco-2 cell line by exerting apoptosis inducing effect (Tan etal., 2019).An endophytic actinomycetes -*Streptomyces sp. BO*-07 from the root tissues of *Boesenbergia rotunda (L.) Mansf A.* had shown maximum activity against *Staphylococcus aureus ATCC25932, Bacillus cereus ATCC7064 and Bacillus subtilis ATCC663.*, and also showed strong antioxidant activity , cytotoxicity against all the three cancer cell lines (HeLa, HepG2 and Huh7) (Taechowisan et.al.2017).The 106 actinomycetes strain isolated from

western Ghat of Tamil Nadu, among them, the both extra cellular ethyl acetate crude extract and intracellular methanol extract *of S. rimosus* (FMS-20) showed good activity against all the tested human pathogenic bacteria, candida and against human fungal pathogens respectively (Ganesan, et.al.2017).

The *Streptomyces strain Al-Dhabi-2* from the thermophilic region kingdom of Saudi Arabia, reported having novel antimicrobial potentials against the pathogenic microorganism (Al-Dhabi et al.2019). The pyrrolo[1,2-a]pyra zine-1,4-dione, hexahydro-3 rich *Streptomyces akiyoshiensis GRG 6 (KY457710)* as a potential anticancer agent against MCF-7 breast cancer cells (Rajivgandhi,et al., 2020), whileLu01-M, a secondary metabolite obtained other *Streptomyces sp*. have potent anti-proliferative activity against prostate cancers. It blocks cell proliferation in human prostate cancer PC3, DU145, and LNCaP cells, both isolated from unexplored marine environment (Lin et.al 2021).Another research reported that 32 isolates from Western Ghats of Karnataka, India were identified as species of *Streptomyces, Nocardiopsis, and Nocardioides*exhibit antimicrobial and antioxidant activity(Siddharth et.al. 2020) .

4. Objectives of research:

- Collection and pedological analysis of soil sample from selected study area.
- Isolation of actinomycetes from collected soil samples.
- Screening and evaluation of bioactive metabolite producing actinomycetes for antimicrobial & anticancer activities.
- Identification of prominent isolates atmolecular level.
- Production and optimization of bioactive molecule
- Characterizationof bioactive molecule
- Quantification of antimicrobial and anticancer activities.

5. Methodology to be adopted :

- **Sample collection:**

  The soil samples will be collected from different regions in Painganga forest by composite random sampling.

- **Pedological analysis** of selected soil sample will be carried out by using standard methods

- **Isolation of actinomycetes** will be carried out by giving various pretreatments to soil and, by using dilution method with various selective medias.

- **Screening for antimicrobial activity :**Screening of actinomycetes for antimicrobial activity against multiple drug resistant bacterial and fungal pathogens will be carried out using agar well diffusion assay.
- **Screening for anticancer activity**

  Anticancer activity of selected isolates will be carried out against MCF-7 cell line by MTT assay.
- **Identification of isolates:**

  Identification of prominent isolates will be carried out on the basis of morphological, biochemicalcharacteristicand at molecular level by 16s rRNA sequencing.
- **Production**of bioactive metabolite from selected potential isolate will be carriedout in optimised media based on various nutritional and cultural parameters.
- **Characterization**of selected bioactive molecules will be carried out using standard analytical techniques including FTIR, GC-MS analysis .
- **Quantification of antibacterial and anticancer activities** of selected bioactive metabolites will be carried out using standard analytical techniques.

6. Importance of studies :

Infectious diseases and cancer are major health care burden around the globe. Numerous causes are responsible for the emergence of drug resistant strains and antimicrobial treatment for rising multidrug resistant bacteria and fungal infections is severely limited. Considering the urgent need for novel antibiotic breakthroughs to combat antimicrobial resistance, in present study actinomycetes isolated from under investigated soils of Painganga forest region will be screened for their broad spectrum antimicrobial and anticancer potential. Potent strains will be identified and the bioactive compound production process will be optimized following which the structural concentration of active metabolite will be carried out to understand possible mechanism of action. The study will reveal tremendous potential of actinomycetes from this untouched forest ecosystem for future drug discovery.

- **International status:**

Osama , et.al.(2022) reported a major group of actinomycetes -the *Streptomycete*s have broad spectrum antimicrobial activity against both gram positive

and gram negative microbes and also have anticancer activity against breast cancer cell line MCF-7 and some strain against hepatoma cell line hepatoma G2 (Hep G2).

Several research groups of China have isolated diverse mangrove actinomycetes and identified them as promising and productive sources of novel bioactive compounds(Xiao et.al.,2009; Guan et al.,2005; Cui et al.,2007).

Elsayed et al., (2020) studied antimicrobial and anticancer activities of actinomycetes isolated from Egyptian soils and found broad spectrum inhibitory effect of *Streptomycetes* sp. in addition to LC_{50} of 1122 µg/ml against Human Lung Cancer cell line (AS49).

National status:

The *Streptomyces* sp. HSN-01produces the active metabolite pyraclostrobin exhibited maximum antimicrobial potential with 17.0, 13.33, 17.66, 15.66, 14.66, and 14.0 mm of inhibition against *B. cereus*, *S. aureus*, *E. coli*, *P. aeruginosa*, *S. flexneri*, and *C. glabrata*and anticancer activity against the hepatocellular carcinoma (HepG2) cell line with IC_{50} 56.76 µg/mL(Math, et.al.,2023). Bundale et al.(2018) reported the isolation of rare culturable non S*treptomyces* from Indian forest soil possessing antitumor activity on the basis of potency and diversity of bioactivity ,isolate KCR3 and NCD10 found to be most potent against Hella cell line.

Recently, Mujumdar et al.,(2023)reported *Streptomyces atrovirens PBR 11* from rhizosphere soil of Pobitora wild life sanctuary Assam, India. The study indicates antimicrobial efficacy of PBR11Fr-1 against *E.coli* and *Candida albicans.* Similarly, Sengupta et al., (2015)reported antimicrobial activities of actinomycetes isolated from unexplored regions of Sundarbans mangrove ecosystem. Sharma and Thakur(2020) revealed antimicrobial biosynthetic potential and diversity of culturable soil actinobacteria from forest ecosystem of Northeast India.

7. Proposed work plan/ formulation and structure of study:

Year wise plan of work and targets to be achieved

❖ **First Year (2022-23):**

- Completion of course work and literature survey
- Sample collection and pedological analysis
- Isolation of actinomycetes

❖ **Second Year (2023-24)**

- Screening and evaluation of bioactive metabolite producing actinomycetes for antimicrobial & anticancer activity
- Identification of prominent isolates at molecular level
- Production of bioactive metabolite from selected isolates

❖ **Third year (2024-25)**

- Characterization of bioactive metabolite obtained from selected isolate
- Quantification of anticancer activity
- Preparation and submission of research article to reputed national and international journal
- Compensation and analysis of data
- Submission of thesis to the university

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